PCT/SE99/01031

09/367950

PRV

PATENT- OCH REGISTRERINGSVERKET
Patentavdelningen

SE99/01031 5000

09/367950

REC'D 09 AUG 1999
WIPO PCT

Intyg
Certificate

Härmed intygas att bifogade kopior överensstämmer med de handlingar som ursprungligen ingivits till Patent- och registreringsverket i nedannämnda ansökan.

Ansökan ingavs ursprungligen på engelska.

This is to certify that the annexed is a true copy of the documents as originally filed with the Patent- and Registration Office in connection with the following patent application.

The application was originally filed in English.

(71) *Sökande* / *Applicant (s)* — *Astra AB, Södertälje SE*

(21) *Patentansökningsnummer* / *Patent application number* — *9802073-8*

(86) *Ingivningsdatum* / *Date of filing* — *1998-06-11*

Stockholm, 1999-07-20

För Patent- och registreringsverket
For the Patent- and Registration Office

Evy Morin

Avgift
Fee

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

PATENT- OCH REGISTRERINGSVERKET
SWEDEN

Postadress/Adress
Box 5055
S-102 42 STOCKHOLM

Telefon/Phone
+46 8 782 25 00
Vx 08-782 25 00

Telex
17978
PATOREG S

Telefax
+46 8 666 02 86
08-666 02 86

NEW USE

Field of the invention

The present invention relates to use of a composition of pharmaceutically active ingredients for the manufacture of a medicament for treatment of asthma as well as a method for treatment of asthma. More particularly the invention relates to the treatment of an acute condition of asthma.

Background to the invention

Despite recent advances in the awareness of asthma and the introduction of powerful and effective anti-asthma drugs, asthma remains a poorly understood and frequently poorly treated disease. There have been recent advances in the treatment of the disease which result from the recognition that asthma is a chronic inflammatory disease. Therapy is now aimed at both controlling the symptoms and reducing the inflammation. The symptoms may be controlled by β_2-adrenoceptor agonists such as terbutaline, salbutamol, formoterol and salmeterol. Prophylactic therapy is typically provided by steroids such as beclo - methasone dipropionate, fluticasone propionate, mometasone furoate and budesonide. In spite of modern maintenance treatment too many asthmatic patients are undertreated for a number of reasons with a negative impact on their quality of life. Too complicated therapy with different medications and devices may lead to miss-understanding and communication problems between patient and doctor. Poor compliance is a common phenomenon. Improved patient education may partly counteract this, but does not completely solve the problem. A new and more simple approach to asthma treatment could thus be of tremendous help for many patients suffering from respiratory disease, particularly asthma. The combination of budesonide and formoterol in the same device as suggested in our PCT applications WO 93/11773 and WO 97/15280 offers a favourable pathway to improve todays asthma management with an excellent safety profile. However, although having an adequate regular, e.g. bid, treatment with such a combination, many

patients will now and then run into acute situations with a higher frequency and severity of exacerbations, when additional medication is needed. Such an additional medication is often a β_2-adrenoceptor agonist with fast onset, normally terbutaline or salbutamol. A second medicament is thus needed, and this can negatively affect the overall compliance of the patient. There is thus need for a neat way of handling maintenance treatment together with the treatment of acute situations.

Accordingly it is an object of the present invention to provide use of suitable compounds for the manufacture of a medicament for the treatment of acute episodes of asthma as a complement to maintenance treatment.

It is a further object of the invention to present a method for treatment of patients suffering from acute asthma.

Summary of the invention

The objects of the invention are obtained by the use and the method as claimed in the claims.

According to the invention there is provided use of a composition comprising, in admixture

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and

(b) a second active ingredient which is budesonide;

for the manufacture of a medicament for use in the acute (as opposed to regular) treatment of asthma, when needed, or for prevention of such a condition.

We contemplate preventive use when the patient expects to encounter asthma inducing conditions e.g. intends to take exercise or go into smoky conditions.

According to a further aspect of the invention a method of treating an acute condition of asthma, when needed, or for prevention of such a condition, is provided. The method

comprises administering, by inhalation, to a patient an effective amount of a composition comprising, in admixture:

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and

(b) a second active ingredient which is budesonide.

According to the present invention it has surprisingly been found that the medicament can be administered when needed to a patient with an acute attack of asthma.

The recommended dose regimen described in the prior art as disclosed above is twice a day. This dose recommendation was a result of a concern not to have too high an administration of the active compounds. However, in the present invention it has been found that it is possible for the patient to administer this mixture as often as needed.

The combination of formoterol and budesonide can be used as a rescue medication. Worsening of symptoms can be counteracted by incremental use of the combination for symptom relief, e.g. during exacerbations with the additional steroid component coming in as early as possible to suppress the enhanced airway inflammation. The long duration of formoterol will reduce the risk of too frequent dosing. When taking the combination budesonide/formoterol when needed the severity of exacerbations can be reduced. The as needed use (*pro re nata*, prn) will also minimize the difficulty of predicting which patients will be controlled on a low dose of inhaled steroid rather than increasing the steroid dose before adding a long-acting β_2-agonist. Under-treatment with inhaled glucocorticosteroids following a too low maintenance dose will be more or less "self-corrected" by the rescue usage according to the present invention. The prn use of the combination will always give some beneficial anti-inflammatory effects even if it is used by the patient only for rescue purposes. A treatment for patients suffering from respiratory disease, particularly asthma (including allergic conditions, e.g. episodic or intermittent asthma), will therefore be to use the combination formoterol/budesonide for maintenenace therapy as well as on an as

needed basis (for rescue purposes), e.g. for prevention of exercise and/or allergen induced asthma.

Detailed description of the invention

Suitable physiologically salts of formoterol include acid addition salts derived from inorganic and organic acids such as the hydrochloride, hydrobromide, sulphate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, methanesulphonate, ascorbate, salicylate, acetate, succinate, lactate, glutarate, gluconate, tricarballylate, hydroxy-naphthalene-carboxylate or oleate. Formoterol is preferably used in the form of its fumarate salt and as a dihydrate of this salt.

The intended dose regimen is thus when needed, an unit dose of formoterol (as fumarate dihydrate) in the range of 3 to 24 µg, preferably between 3 to 12 µg, with a maximum daily dose, including maintenance therapy, of 60 µg.

A suitable unit dose of budesonide is in the range of 50 to 400 µg, preferably between 100 to 400 µg, with a maximum daily dose, including the maintenance therapy, of 3200 µg. The particular dose regimen will depend on the patient (age, weight etc) and the severity of the disease (mild, moderate, severe asthma etc).

The molar ratio of the first active ingredient (as formoterol) to the second active ingredient in the invention is preferably from 1:1 to 1:100.

Preferably the mixture comprises one or more pharmaceutically acceptable additives, diluents or carriers, more preferably in an amount of from 50 to 4000 µg in each dose, most preferably in an amount of from 100 to 2000 µg and most preferably from 100 to 1000 µg. Examples of suitable additives, diluents or carriers include lactose, dextran, mannitol or glucose. Preferably lactose is used, and more preferably as the monohydrate.

One or more of the ingredients of the mixture may be in the form of dry powder, more preferably a small particle dry powder, most preferably an agglomerated small particle dry powder. Alternatively one or more of the active ingredients (a) or (b) are in the form of an ordered mixture with diluent, additive or carrier. The ingredients used in the invention can be obtained in these preferred forms using methods known to those skilled in the art. The particle size of the active ingredients is preferably less than 10 µm.

Administration may be by inhalation orally or intranasally. The ingredients of the system are preferably adapted to be administered from a dry powder inhaler, a pressurized metered dose inhaler , or a nebulizer.

When the ingredients of the system are adapted to be administered from a pressurized inhaler, they are preferably in a small particle form. They are dissolved, or, preferably, suspended in a liquid propellant mixture. The propellants which can be used include chlorofluorocarbons, hydrocarbons or hydrofluorocarbons. Especially preferred propellants are P134a (tetrafluoroethane), P152a (difluoroethane) and P227 (heptafluropropane) each of which may be used alone or in combination. They are optionally used in combination with one or more other propellants and/or one or more surfactants and/or one or more other excipients, for example ethanol, a lubricant, an antioxidant and/or a stabilizing agent.

When the ingredients of the system of the invention are adapted to be administered via a nebulizer they may be in the form of a nebulized aqueous suspension or solution, with or without suitable pH or tonicity adjustment, either as a unit dose or multidose formulation.

The ingredients can be formulated as illustrated by the following examples which are not intended to limit the scope of the application. In the examples micronization is carried out in a conventional manner such that the particle size range for each component is suitable for administration by inhalation. Turbuhaler® is a trademark of Astra AB.

Example 1

4.5 Parts by weight of formoterol fumarate dihydrate were mixed with 915 parts by weight of lactose monohydrate. The blend was micronized using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 80 Parts by weight of micronized budesonide were added to the conditioned product by mixing and homogenizing with a low pressure jet mill. The mixture was then spheronized using the process of EP-A-721 331 and filled into the storage compartment of Turbuhaler.®

Example 2

9 Parts by weight of formoterol fumarate dihydrate were mixed with 831 parts by weight of lactose monohydrate. The blend was micronized using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 160 Parts by weight of micronized budesonide were added to the conditioned product by mixing and homogenizing with a low pressure jet mill. The mixture was then spheronized using the process of EP-A-721 331 and filled into the storage compartment of Turbuhaler.®

Example 3

6 Parts by weight of formoterol fumarate dihydrate were mixed with 894 parts by weight of lactose monohydrate. The blend was micronized using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 100 Parts by weight of micronized budesonide were added to the conditioned product by mixing and homogenizing with a low pressure jet mill. The mixture was then spheronized using the process of EP-A-721 331 and filled into the storage compartment of Turbuhaler.®

Example 4

12 Parts by weight of formoterol fumarate dihydrate were mixed with 788 parts by weight of lactose monohydrate. The blend was micronized using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 200 Parts by weight of micronized budesonide were added to the conditioned product by mixing and homogenizing with a low pressure jet mill. The mixture was then spheronized using the process of EP-A-721 331 and filled into the storage compartment of Turbuhaler®.

Example 5

A patient on maintenance treatment with the fixed combination formoterol fumarate dihydrate/budesonide in a dose of 4.5/80 µg or 4.5/160 µg bid additionally uses the same combination either for rescue purposes once or twice daily to treat sporadic breakthrough symptoms, or as needed to treat exacerbations during one or two weeks, with a maximum daily dose of 36/640 µg (8 puffs of 4.5/80 µg) and 36/1280 µg (8 puffs of 4.5/160 µg) respectively.

Example 6

A patient with intermittent asthma uses the fixed combination formoterol fumarate dihydrate/budesonide as sole medication to be taken as needed until the asthma resolves. The highest recommended daily dose will be either 36/640 µg (8 puffs of 4.5/80 µg) or 36/1280 µg (8 puffs of 4.5/160 µg) for a period not exceeding 8-120 weeks. If symptoms still persist after that period of time - regular maintenance therapy should be considered.

Claims

1. Use of a composition comprising, in admixture:

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt; and

(b) a second active ingredient which is budesonide;

for the manufacture of a medicament for use in the treatment of an acute condition of asthma, when needed, or for prevention of such a condition.

2. Use according to claim 1, wherein the molar ratio of (a) to (b) is from 1:1 to 1:100.

3. Use according to claim 1 or 2, wherein the first active ingredient is formoterol fumarate dihydrate.

4. Use according to claim 1, 2 or 3, wherein the composition additionally comprises one or more pharmaceutically acceptable additives, diluents or carriers.

5. A method of treating an acute condition of asthma, when needed, or for prevention of such a condition, which comprises administering, by inhalation, to a patient an effective amount of a composition comprising, in admixture:

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and

(b) a second active ingredient which is budesonide.

6. A method according to claim 5 wherein the molar ratio of (a) to (b) is from 1:1 to 1:100.

7. A method according to claim 5 or 6, wherein the first active ingredient is formoterol fumarate dihydrate.

8. A method according to claim 5, 6 or 7, wherein the composition additionally comprises one or more pharmaceutically acceptable additives, diluents or carriers.

Abstract

There is described use of a composition comprising, in admixture:

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt; and

(b) a second active ingredient which is budesonide;

for the manufacture of a medicament for use in the treatment of an acute condition of asthma, when needed, or for prevention of such a condition.